Dose Proportionality of Once-Daily Trazodone Extended-Release Caplets Under Fasting Conditions

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An extended-release trazodone HCl formulation, Trazodone Contramid OAD (TzCOAD), was developed as scored 150-mg and 300-mg caplets for once-daily administration. Dose proportionality of intact and bisected caplets (dose range, 75-375 mg) was evaluated in a single-dose, randomized, 5-way crossover study. Plasma trazodone and m-chlorophenylpiperazine (mCPP) levels were determined using a validated liquid chromatography–tandem mass spectroscopy method. Dose proportionality was assessed based on confidence intervals for logarithmically transformed, dose-normalized maximum plasma concentration (C_{max}), area under the plasma concentration versus time data pairs (AUC_{0-t}), and area under the curve from time 0 to infinity ($AUC_{0-\infty}$) in relation to the acceptance range of 80% to 125% (bioequivalence approach). The power method, combined with confidence interval criteria, was also used to assess proportionality. The conclusion of dose proportionality was generally supported using the bioequivalence approach. Based on the power model, values of the slope and corresponding 90% confidence interval for trazodone C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were 0.948 (0.899-0.997), 0.920 (0.875-0.964), and 0.913 (0.867-0.958), respectively. All were within the acceptance interval (0.861-1.139). Results for mCPP also fell within the acceptance interval. TzCOAD exhibits linear pharmacokinetics over doses ranging from 75 to 375 mg and maintains its controlled-release properties when the caplets are bisected along the score line.

Keywords: *Trazodone; m-chlorophenylpiperazine; pharmacokinetics; dose proportionality; power model*

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Trazodone is a second-generation triazolopyridine derivative that is chemically and pharmacologically distinct from other classes of antidepressants such as selective serotonin reuptake inhibitors, tri- and tetracyclics, and monoamine oxidase inhibitors.[1,2] It has been commercially available in the United States since 1982.[3] Trazodone acts through combined serotoninergic (5-HT_{2a} and 5-HT_{2c}) receptor antagonism and serotonin reuptake inhibition.[4] Trazodone is a moderately to highly potent α-adrenoceptor antagonist, has moderate antihistaminergic (H_1) activity, and possesses anxiolytic and hypnotic properties.[1,5]

After oral administration, trazodone is rapidly and almost completely absorbed.[6,7] When immediate-release trazodone tablets are administered under fasting conditions, peak plasma trazodone concentrations are attained in 0.5 to 2 hours.[8] Trazodone undergoes extensive hepatic metabolism by hydroxylation, dealkylation, and *N*-oxidation,[9] with less than 1% of an oral dose excreted unchanged in the urine.[10,11] Twenty percent of a trazodone dose is metabolized to a pharmacologically active metabolite, *m*-chlorophenylpiperazine (mCPP), by *N*-dealkylation via the cytochrome P450 isoenzyme CYP3A4.[9] The active metabolite then undergoes 4′-hydroxylation to *p*-hydroxy-mCPP via CYP2D6.[12] Plasma concentrations of mCPP range from 1% to 20% those of the parent drug following oral administration of trazodone HCl.[9] Trazodone exhibits biphasic elimination with a mean distribution half-life of 3 to 6 hours and an elimination half-life of 5 to 9 hours.[13] Others have reported mean trazodone elimination half-life values ranging from 4.1 hours[14]

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Table I Similarity Factors for 150-mg and 300-mg Intact and Bisected TzCOAD Caplets Under Various Test Conditions

Strength, mg	Dissolution Medium, pH Level	Duration, h	f_2 Intact vs Half Caplet	f_2 Intact vs 2 Half Caplets
150	1.2/6.0	1 /23	57.5	70.7
	1.2	24	58.2	69.4
	4.0	24	60.9	67.8
	6.0	24	57.7	73.9
300	1.2/6.0	1/23	67.4	71.2
	1.2	24	54.4	65.6
	4.0	24	75.0	87.9
	6.0	24	57.7	66.2

Apparatus: Type II USP; agitation rate: 150 rpm; temperature: 37 ± 0.5°C.

to 14.6 hours[15] following single-dose administration of immediate-release trazodone tablets in healthy adult subjects. Approximately 70% of an oral dose of trazodone in humans is recovered in the urine within 72 hours, and the remainder is excreted in the feces.[7]

Drawing on limited data, Preskorn[16] suggested that trazodone may have nonlinear pharmacokinetics due to saturation of its first-pass metabolism as doses are increased over the clinically relevant dosing range, leading to speculation that maximum plasma concentration (C_{max}) could increase exponentially with increasing doses. Conversely, Nilsen et al[17] reported that the pharmacokinetics of trazodone are linear over doses ranging from 100 to 300 mg/d.

The half-life of trazodone (ie, 5-9 hours) is relatively short for an antidepressant.[16] Therefore, multiple daily doses are standard with trazodone immediate-release products. This requirement can be inconvenient for patients, resulting in decreased compliance—particularly in patients with more than mild depression—thereby decreasing the drug's overall antidepressant effectiveness.[16] Moderate to high doses are required for trazodone to be an effective antidepressant.[5] However, the rapid rise and high peak in plasma concentrations likely contribute to the intolerable or unacceptable somnolent/sedating effects that limit the use of immediate-release trazodone as an antidepressant.[18,19]

Reformulating the drug to control the rate of release of trazodone may improve tolerability by avoiding the early and relatively high peak plasma concentrations of the conventional immediate-release formulations. An added benefit of a once-daily formulation is a reduction in dosing frequency. Such a formulation could be administered as a single dose at bedtime to mitigate the adverse effects associated with immediate-release trazodone, improve sleep, and reduce or eliminate daytime drowsiness, while exploiting the beneficial sedating effects of the drug.

Trazodone Contramid OAD (TzCOAD), an extended-release, once-daily formulation of trazodone HCl developed by Labopharm (Laval, Quebec, Canada), is designed to optimize the antidepressant efficacy of trazodone. Contramid, a proprietary drug-delivery technology based on chemically cross-linked high amylose starch, controls the release of trazodone from the dosage form over an extended period. Gastric fluids transform the surface of the tablet into a gel, through which drug diffuses at a constant rate.[20] TzCOAD was developed as 150- and 300-mg trazodone HCl scored caplets that can be bisected to provide flexibility in dosing. Dosing is initiated at 150 mg and titrated by 75-mg increments to a maximum daily dose of 375 mg.

The main advantage of modified-release dosage forms is that relatively stable drug blood concentrations can be maintained at therapeutic levels over long periods of time following each administration, thereby avoiding the multiple peaks and troughs associated with administration of immediate-release formulations. To be divisible, a modified-release formulation must maintain its controlled-release characteristics (ie, dose dumping does not occur when tablets are bisected). TzCOAD caplets are designed so that splitting the tablet along the score line does not significantly affect drug release. Dissolution profiles were generated for 150-mg and 300-mg caplets in 4 media for each of the following: ½ unit, 2 × ½ unit, and 1 intact unit. The dissolution profiles of bisected and intact caplets in the various media were compared and the resulting similarity factors are presented in Table I. The 24-hour profiles were

similar for whole and bisected caplets regardless of the media used.

A dose proportionality study was conducted to compare the bioavailability of intact and bisected TzCOAD 150- and 300-mg extended-release caplets following single-dose administration of doses ranging from 75 to 375 mg. As specified in the study protocol, 2 methods were used to assess dose proportionality: the bioequivalence approach and the power model method.

METHODS

Subjects

Healthy, nonsmoking adult male and female subjects were clinically evaluated for eligibility within 14 days before the study commenced. This included a physical examination; hematological and clinical chemistry evaluation; screening for HIV antibodies, hepatitis B surface antigens, and hepatitis C antibodies; a pregnancy test; 12-lead electrocardiogram (ECG); vital signs; urinalysis; and a urine screen for drugs of abuse and cotinine. Given the volume of blood to be drawn, body weight below 65 kg was an exclusion criterion.[21]

Study Design

This was an open-label, laboratory-blind, single-dose, randomized, 5-period crossover study conducted under fasting conditions. The study was designed to detect a 20% difference in key parameter values (ie, area under the plasma concentration-time curve [AUC] and C_{max}) for the parent drug with 80% power based on the known pharmacokinetic variability for the intact caplet. Subjects were admitted to the clinic on the evenings before the profile days to ensure a fasting period of at least 10 hours and were allowed to leave the research facility 48 hours after drug administration.

Study phases were separated by 7-day drug-free washout periods between consecutive administrations of study medication. Subjects were not allowed to take any medication, including over-the-counter drugs, for 14 days preceding the study and during the study (except if, in the opinion of the investigators, this would not affect the outcome of the study). The ingestion of food and beverages containing citrus fruits, apple, or pineapple was not allowed for 72 hours prior to drug administration and during treatment periods. Alcohol and methylxanthines were restricted for 24 hours before drug administration and during treatment periods. Strenuous physical activity was not permitted for 24 hours before the start of each clinic stay and until 72 hours after administration of study medication.

Ethical and Regulatory Compliance

The study was conducted in accordance with the 2004 revision of the Declaration of Helsinki (Tokyo)[22]; the 2002 ICH Guideline for Good Clinical Practice[23]; the Note for Guidance on the Investigation of Bioavailability and Bioequivalence[24]; the Guidance for Industry: Bioavailability and Bioequivalence Studies for Orally Administered Drug Products—General Considerations[25]; the Medicines Control Council (of South Africa) Registration of Medicines, Biostudies, version 1, 2003[26]; the 2000 Clinical Trials Guidelines of the Department of Health of South Africa[27]; in-house standard operating procedures; and local legal requirements. Before the study commenced, the protocol was approved by the South African Medicines Control Council and the Ethics Committee of the Faculty of Health Sciences of the University of the Free State, South Africa, and all subjects gave written informed consent. Internal and external monitoring and auditing were carried out throughout the study.

Study Treatment

The randomization schedule, following a Williams design, was generated with RANDPLAN (version 1.0), using the PROC PLAN procedure in SAS (SAS Institute, Cary, NC).[28] The following treatments were investigated: ½ × 150-mg caplet (75-mg dose); 1 × 150-mg caplet (150-mg dose); ½ × 300-mg caplet (150-mg dose); 1 × 300-mg caplet (300-mg dose); and 1 × 300-mg + ½ × 150-mg caplet (375-mg dose). Halving the caplets to obtain correct doses was performed according to Labopharm standard method no. A041, version 01, at the dispensing unit of the contract research organization by a qualified pharmacist. Study medication administered on treatment days was retained in a single separate container for each subject for each treatment. Subjects received a single dose of 75, 150, 300, or 375 mg of trazodone HCl with 240 mL of water under fasting conditions, according to the randomization schedule. Subjects continued to fast for an additional 5 hours after each dose. Except for ingestion of a meal 5 hours post dose, and voiding as needed,

subjects remained recumbent for 8 hours after drug administration. Thereafter, no restrictions regarding posture or movement applied. During housing, meals were standardized and conformed to a Western diet. Fluid administration was also standardized. After 48 hours post dose, the restrictions on food and fluid intake were lifted. Blood samples for the poststudy laboratory safety investigation were collected within 72 hours after completion of the study.

Sample Collection

Blood samples, 5 mL each, were collected from an indwelling venous cannula or venipuncture into heparinized, labeled plastic tubes according to the following time schedule: before drug administration and at 0.5, 1, 2, 3, 4, 5, 6, 8, 9, 10, 11, 12, 14, 16, 20, 24, 30, 36, 48, and 72 hours thereafter. Blood samples were immediately placed on ice and, within 1 hour of collection, were centrifuged at 2700*g* for 10 minutes at approximately 4°C; the supernatant was transferred to labeled plastic tubes. Duplicate aliquots were stored at approximately –80°C pending trazodone and mCPP assays.

Analytical Methods

Plasma concentrations of trazodone and mCPP were determined using a validated liquid chromatography–tandem mass spectroscopy (LC-MS/MS) method. The method makes use of liquid–liquid back extraction followed by high-performance liquid chromatography (HPLC) with tandem mass spectrometric detection. Domperidone ($C_{22}H_{24}ClN_5O_2$, MW 425.92) was used as the internal standard. A Supelco Discovery C_{18} (150 × 2.1 mm, 5 µm) HPLC column was used with acetonitrile/methanol/0.1% formic acid (5:35:60, vol/vol/vol) as the mobile phase. The flow rate was 250 µL/min. The transition ions at m/z 372 → 176 and at m/z 197 → 154 were monitored for trazodone and mCPP, respectively. Labopharm, Inc supplied the reference standards (trazodone and mCPP raw material) and certificates of analysis.

Pharmacokinetic Analysis

Pharmacokinetic variables were determined using WinNonlin Professional 5.0.1 (Pharsight, Mountain View, Calif). The C_{max} and the time to maximum plasma concentration (T_{max}) were read directly from the observed concentration data. The apparent terminal elimination half-life ($t_{1/2}$) was calculated from the nonlinear regression of a single exponential function (Ce^{-zt}) to the terminal phase of the untransformed plasma concentration versus time profile, where z is the apparent terminal elimination rate constant. The regressions were done using the method of nonlinear least squares. The terminal half-life was then calculated as $t_{1/2} = (\ln 2)/z = 0.693/z$. The AUC was calculated according to the linear trapezoidal rule from time 0 to the time of the last quantifiable concentration after drug administration ($AUC_{0\text{-}t}$). $AUC_{0\text{-}t}$ was extrapolated to infinity by adding C(t)/z. Thus $AUC_{0\text{-}\infty} = AUC_{0\text{-}t} + C(t)/z$, where $AUC_{0\text{-}\infty}$ is the area under the curve from time 0 to infinity, z is the apparent terminal elimination rate constant, and C(t) is the last quantifiable concentration.

Statistical Analysis

Bioequivalence approach. The dose-proportionality assessment using the bioequivalence approach was based on 5 comparisons:

1. 1 × 150-mg caplet vs 1 × 300-mg caplet
2. ½ × 150-mg caplet vs 1 × 150-mg caplet
3. ½ × 300-mg caplet vs 1 × 300-mg caplet
4. ½ × 150-mg caplet vs 1 × 300-mg caplet
5. ½ × 150-mg + 300-mg caplet vs 1 × 300-mg caplet

The dose-dependent parameters (C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$) were normalized to 300 mg and designated as C_{max}norm, $AUC_{0\text{-}t}$norm, and $AUC_{0\text{-}\infty}$norm: these were the primary variables investigated for the assessment of dose proportionality.

The 5 treatments were compared with respect to the ln-transformed pharmacokinetic parameters C_{max}norm, $AUC_{0\text{-}\infty}$norm, and $AUC_{0\text{-}t}$norm for trazodone and mCPP using an analysis of variance (ANOVA) with sequence, treatment, and period as fixed effects and subject nested within sequence as a random effect. Point estimates and 90% confidence intervals for the test/reference mean ratio of these variables were calculated.

Dose proportionality was assessed on the basis of the confidence interval for the variables C_{max}norm, $AUC_{0\text{-}t}$norm, and $AUC_{0\text{-}\infty}$norm in relation to the predefined conventional acceptance range of 80% to

Table II Subject Demographics (N = 45)

	Age, y	Height, cm	Weight, kg	Body Mass Index, kg/m^2
Mean ± SD	29.6 ± 11.1	175.9 ± 9.3	75.0 ± 8.0	24.3 ± 2.2
Range	19-52	162-200	65.0-103.4	19.8-28.6

125%.[29] In addition, a Wilcoxon signed rank test was performed on T_{max}.

The parametric statistical analysis (ANOVA, conventional point estimates, and confidence interval)[30] was performed using the general linear models procedure (PROC GLM) of SAS 8.2.[28] The nonparametric statistical analysis of T_{max} was performed using a SAS macro according to the method described by Steinijans and Diletti[31] and Hauschke et al.[32]

Power model. At the request of the US Food and Drug Administration (FDA), the power model, as described by Gough et al[33] using the modification of Smith et al,[34] was also used to assess the dose proportionality of C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$. A mixed-effects statistical model, allowing for random between-subject variability in the intercept and slope parameters, was implemented to estimate the proportionality constant, β, and its corresponding 90% confidence interval. Log(Y) versus log(Dose), where Y = C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$, was fitted using a purpose-written script in S-PLUS 6.2 (Insightful Corporation, Seattle, Wash). The statistical model included terms for subject and dose. Values of β and its corresponding 90% confidence interval were estimated and compared with the modified acceptance intervals using the following decision rules: (1) dose proportionality was declared if the calculated 90% confidence interval for β lay entirely within the acceptance range [1 + (log(θ_L) / (log(r)), 1 + (log(θ_H) / (log(r))], where θ_L and θ_H are the lower and upper limits of the confidence interval and r is the maximal dose ratio for the study; (2) lack of proportionality was concluded if the calculated 90% confidence interval lay completely outside the acceptance region; (3) results with respect to dose proportionality were determined to be inconclusive if the calculated 90% confidence interval spanned the acceptance region.[34]

Both methods for assessing dose proportionality were specified in the protocol, and the protocol was finalized prior to the first administration of study medication. For the power model assessment, the values of θ_L and θ_H were not predefined in the protocol. However, the same values were used as for the bioequivalence approach (ie, 0.80 and 1.25, respectively). No changes were made to the planned statistical analyses after the protocol was finalized.

Safety Analysis

Subjects were monitored for adverse events throughout the study. Body temperature, heart rate, and blood pressure were recorded before drug administration, and the latter 2 measurements were repeated at 1, 2, 4, 6, 10, 12, 14, 16, and 48 hours after drug administration. A 12-lead ECG was performed at 6 and 12 hours post dose. Results from the poststudy physical examination, clinical laboratory assessments, vital signs assessment, and ECG were evaluated for changes in health status. Subjects withdrawn from the study were given appropriate follow-up care.

RESULTS

Clinical Observations

Forty-five healthy adult Caucasian subjects (25 men and 20 women) were enrolled in the study. Two male subjects were withdrawn by the principal investigator: 1 subject during treatment phase 1 because of an adverse event (vomiting approximately 3.5 hours after receiving a 1 × 150-mg dose) that could have affected the pharmacokinetic assessment, and 1 subject before the fifth treatment phase commenced because of a protocol violation (the subject received all treatments except the ½ × 150-mg dose). Demographic data of the subjects enrolled in the study are presented in Table II.

The remaining subjects completed all 5 treatment phases. All subjects tested negative for HIV antibodies, hepatitis B surface antigens, and hepatitis C antibodies. The subjects also had negative urinalysis results for protein and bilirubin. Results for drugs of abuse (benzodiazepines, opiates, cannabinoids, and cotinine) were negative, with the exception of 1 subject who was consequently withdrawn from the study. Pregnancy tests on admission during all treatment phases and post study were negative.

All 45 subjects received at least 1 dose of study medication and therefore comprised the safety

Table III Number (Percentage) of Subjects Reporting Trazodone-Related Adverse Events

Adverse Event	½ × 150 mg (n = 43)	1 × 150 mg (n = 45)	½ × 300 mg (n = 44)	1 × 300 mg (n = 44)	½ × 150 mg + 1 × 300 mg (n = 44)
Headache	2 (4.7)	4 (8.9)	8 (18.2)	7 (15.9)	6 (13.6)
Dizziness	1 (2.3)	1 (2.2)	1 (2.3)	6 (13.6)	8 (18.2)
Nausea	–	2 (4.4)	1 (2.3)	2 (4.5)	2 (4.5)
Syncope	–	–	–	–	3 (6.8)
Musculoskeletal pain	–	2 (4.4)	–	1 (2.3)	1 (2.3)
Paresthesia	–	–	–	1 (2.3)	1 (2.3)
Somnolence	–	–	–	1 (2.3)	1 (2.3)
Vomiting	–	1 (2.2)	–	–	–
Insomnia	–	1 (2.2)	–	–	–
Malaise	–	–	–	1 (2.3)	–
No. of subjects reporting an adverse event (most common)	3	8	9	11	18
No. of most common adverse events reported	3	11	13	24	24

The safety analysis included all subjects who received at least 1 dose of study medication. One subject completed 4 treatment phases, and another subject completed only the first treatment phase.

population. Trazodone was well tolerated by all subjects, and no serious adverse events were reported. Eighty-nine adverse events were reported by 29 of 45 subjects (64%). Of these, 72 events (81%) were assessed as at least possibly related to the study medication. The number of reported adverse events increased with dose, and all were rated as mild or moderate in severity. The predominant adverse events were headaches (34 incidences), reported by 14 of 45 subjects (31%) and dizziness (18 incidences), reported by 13 of 45 subjects (29%). The trazodone-related adverse events are summarized in Table III. All of the listed adverse events have been reported previously following administration of trazodone.[35] No adverse events due to laboratory variables, vital signs, or ECGs were reported during the study.

Analytical Results

Plasma trazodone and mCPP levels were determined using an LC/MS-MS method developed and validated at Farmovs-Parexel. Calibration curves were linear according to a Wagner regression curve over the ranges 7.754 to 3969 ng/mL for trazodone and 0.234 to 120 ng/mL for mCPP with $r^2 \geq 0.9994$ and $r^2 \geq 0.9991$, respectively, and covered the observed C_{max} values adequately. The bioanalytical method met the requirements for specificity, sensitivity, accuracy, imprecision, and linearity. Freeze-thaw, on-bench, and on-instrument stabilities were found to be well within predetermined ranges.

Pharmacokinetic Results

Data from 44 subjects who completed at least 2 study periods were included in the data set used for pharmacokinetic analysis. The mean plasma trazodone and mCPP concentration versus time profiles are presented in Figures 1 and 2. The pharmacokinetic parameters and results of the statistical analyses based on the bioequivalence approach are summarized in Tables IV and V. The results of the power assessment for trazodone and mCPP are presented in Table VI.

Following single oral administration of TzCOAD, the median time to reach peak trazodone and mCPP plasma concentrations across dose levels ranged from 6.0 to 9.0 hours post dose and 10.5 to 12.0 hours post dose, respectively. Differences in the time to reach maximum plasma concentrations were not statistically significant for any of the comparisons. The half-life values reported were similar across doses, ranging from 12.0 to 13.2 hours for trazodone and 12.4 to 16.0 hours for mCPP.

Bioequivalence approach. The conclusion of dose proportionality was generally supported based on analysis using the bioequivalence approach. For trazodone, with 1 exception, the treatments were proportional with respect to peak and total systemic exposure. The dose-normalized C_{max} was 19.7% higher for the half 300-mg caplet compared with the intact 300-mg caplet. Thus, dose proportionality could not be concluded because the upper limit of

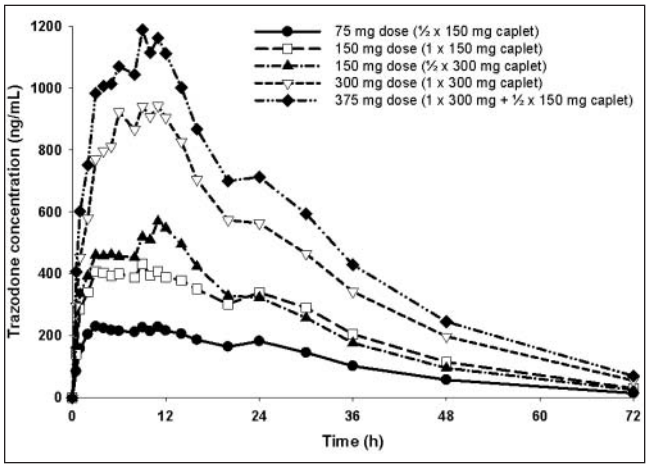

Figure 1. Mean plasma trazodone concentrations following single-dose administration of intact and bisected TzCOAD caplets at doses ranging from 75 to 375 mg. 261 × 186 mm (96 × 96 DPI).

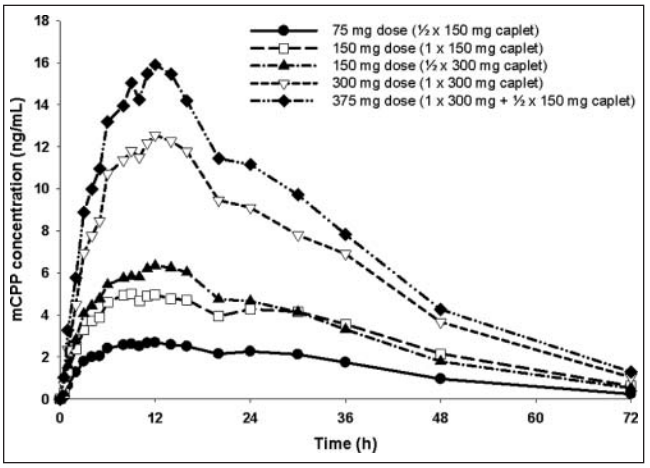

Figure 2. Mean plasma m-chlorophenylpiperazine (mCPP) concentrations following single-dose administration of intact and bisected TzCOAD caplets at doses ranging from 75 to 375 mg. 263 × 180 mm (96 × 96 DPI).

Table IV Pharmacokinetic Parameters and Results of Statistical Analysis of Trazodone (n = 44[a])

Parameter	A (½ × 150 mg)	B (1 × 150 mg)	C (½ × 300 mg)	D (1 × 300 mg)	E (½ x150 + 1 × 300 mg)	Parameter Comparison	Mean Ratio, %[b]	90% CI	*P*
AUC_{0-t}, ng·h/mL	8124 ± 2502	15505 ± 4764	16161 ± 4836	29200 ± 10426	36251 ± 11345	A vs B	104.5	97.9-111.5	
						A vs D	112.2	105.2-119.7	
						B vs D	107.4	100.7-114.5	
						C vs D	112.2	105.2-119.7	
						E vs D	100.8	94.5-107.5	
$AUC_{0-\infty}$, ng·h/mL	8658 ± 2833	16388 ± 5419	16911 ± 5384	30983 ± 12522	38291 ± 13893	A vs B	105.4	98.7-112.6	
						A vs D	113.3	106.1-121.0	
						B vs D	107.5	100.7-114.8	
						C vs D	111.5	104.4-119.0	
						E vs D	100.3	94.0-107.1	
C_{max}, ng/mL	294 ± 71	531 ± 143	677 ± 171	1179 ± 583	1401 ± 522	A vs B	111.3	102.6-120.7	
						A vs D	104.6	96.4-113.4	
						B vs D	94.0	86.7-101.8	
						C vs D	119.7	110.5-129.8	
						E vs D	96.8	89.3-104.9	
$t_{1/2}$, h	12.7 ± 5.3	12.4 ± 6.0	12.0 ± 5.2	13.2 ± 7.9	12.5 ± 5.7	—			
T_{max}, h	8.0 (2.0-30.0)	6.0 (2.0-30.0)	9.0 (1.0-14.0)	7.0 (2.0-14.0)	8.0 (1.0-16.0)	A vs B			.27
						A vs D			.08
						B vs D			.96
						C vs D			.16
						E vs D			.67

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; CI, confidence interval; C_{max}, maximum plasma concentration; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to reach C_{max}. Data are presented as mean ± standard deviation, except for T_{max} values, which are presented as median (range). For T_{max}, the *P* value according to the Wilcoxon signed rank test is presented.

a. For treatment A, 43 subjects were evaluated.

b. Least squares means ratios were calculated on dose-normalized pharmacokinetic variables.

Table V Pharmacokinetic Parameters and Results of Statistical Analysis of *m*-Chlorophenylpiperazine (n = 44[a])

Parameter	A (½ × 150 mg)	B (1 × 150 mg)	C (½ × 300 mg)	D (1 × 300 mg)	E (½ × 150 + 1 × 300 mg)	Parameter Comparison			
						Parameters	Mean Ratio, %[b]	90% CI	*P*
AUC_{0-t}, ng·h/mL	104 ± 108	211 ± 228	223 ± 231	437 ± 463	539 ± 530	A vs B	99.2	91.3-107.7	
						A vs D	96.6	88.9-104.9	
						B vs D	97.4	89.8-105.7	
						C vs D	106.6	98.2-115.7	
						E vs D	102.4	94.3-111.1	
$AUC_{0-\infty}$, ng·h/mL	120 ± 118	235 ± 260	242 ± 263	470 ± 515	576 ± 595	A vs B	107.3	99.0-116.3	
						A vs D	107.1	98.8-116.1	
						B vs D	99.8	92.2-108.2	
						C vs D	107.2	99.0-116.2	
						E vs D	101.6	93.8-110.1	
C_{max}, ng/mL	3.08 ± 2.48	5.76 ± 4.56	7.27 ± 5.12	13.9 ± 12.0	18.2 ± 14.8	A vs B	106.2	96.4-117.0	
						A vs D	91.0	82.6-100.2	
						B vs D	85.7	77.8-94.3	
						C vs D	112.6	102.2-123.9	
						E vs D	102.8	93.4-113.2	
$t_{1/2}$, h	16.0 ± 9.9	13.2 ± 6.5	12.4 ± 5.8	13.6 ± 6.7	12.4 ± 4.4		—		
T_{max}, h	12.0 (3.0-36.0)	11.0 (3.0-36.0)	12.0 (4.0-36.0)	11.5 (4.0-30.0)	10.5 (4.0-30.0)	A vs B			.53
						A vs D			.28
						B vs D			.06
						C vs D			.74
						E vs D			.17

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; C_{max}, maximum plasma concentration; CI, confidence interval; $t_{1/2}$, apparent terminal elimination half-life; T_{max}, time to reach C_{max}. Data are presented as mean ± standard deviation, except for T_{max} values, which are presented as median (range). For T_{max}, the *P* value according to the Wilcoxon signed rank test is presented.

a. For treatment A, 43 subjects were evaluated.

b. Least squares means ratios were calculated on dose-normalized pharmacokinetic variables.

Table VI Summary of Assessment of Dose Proportionality Based on the Power Model

Variable	Acceptance Interval	Trazodone		*m*-Chlorophenylpiperazine	
		β	90% Confidence Interval	β	90% Confidence Interval
AUC_{0-t}, ng·h/mL	0.861-1.139	0.920	0.875-0.964	1.024	0.969-1.079
$AUC_{0-\infty}$, ng·h/mL	0.861-1.139	0.913	0.867-0.958	0.963	0.912-1.013
C_{max}, ng/mL	0.861-1.139	0.948	0.899-0.997	1.068	1.011-1.124

AUC_{0-t}, area under the plasma concentration-time curve from time 0 to the last quantifiable concentration; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time 0 to infinity; β, estimate of the proportionality constant; C_{max}, maximum plasma concentration.

the 90% confidence interval for dose-normalized C_{max} (110.5%-129.8%) was higher than the acceptance limit of 125%.

For mCPP, the treatments were proportional with respect to peak and total systemic exposure, with 1 exception. The dose-normalized C_{max} for mCPP was 14.3% lower for the 150-mg caplet compared with the 300-mg caplet. Thus, dose proportionality could not be concluded for peak mCPP exposure because the lower limit of the 90% confidence interval for dose-normalized C_{max} (77.8%-94.3%) fell below the lower acceptance limit.

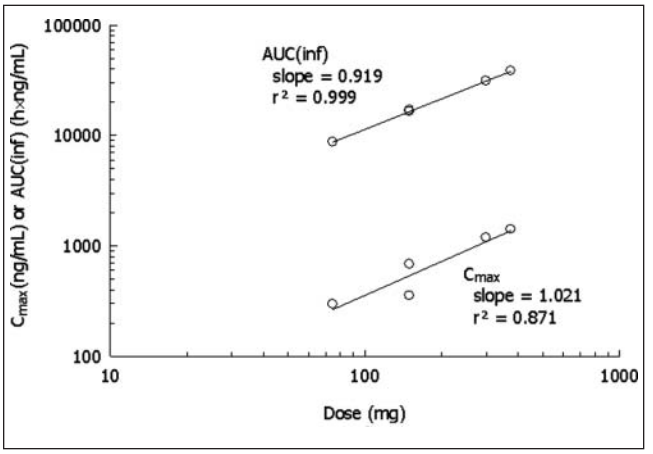

Figure 3. Relationship between the mean extent of trazodone systemic exposure and dose after oral administration of single doses of TzCOAD ranging from 75 to 375 mg to healthy subjects under fasting conditions. C_{max}, maximum plasma concentration; AUC(inf), area under the plasma concentration-time curve from time 0 to infinity. 180 × 116 mm (96 × 96 DPI).

Power model. The relationship between the peak and total trazodone systemic exposure (characterized C_{max} and $AUC_{0-\infty}$) and the administered dose is illustrated in Figure 3. Plots of the fitted function for the power model with associated 90% confidence intervals are presented for C_{max} and $AUC_{0-\infty}$ in Figure 4. Results of the assessment based on the power model (Table VI) showed that the 90% confidence interval for β lay completely within the acceptance region for C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ for both trazodone and mCPP.

DISCUSSION

Dose proportionality can be expressed as a doubling of the dose resulting in a doubling of the peak (C_{max}) or total (AUC) systemic exposure.[34] A lack of proportionality can result from intrinsic factors related to the drug substance (eg, saturable absorption, saturable metabolism) or from extrinsic factors related to the drug product (eg, different tablet strengths with different release rates). The clinical consequence of nonproportionality is a loss of predictability when adjusting the dosage.[33] Several methods are available to assess dose proportionality. The bioequivalence approach involves analysis of variance of ln-transformed dose-normalized parameters, followed by pairwise comparisons between doses. Estimates of the size of the difference in parameter values between doses can be readily obtained, along with confidence intervals. This approach is easy to apply and to understand and makes no assumptions

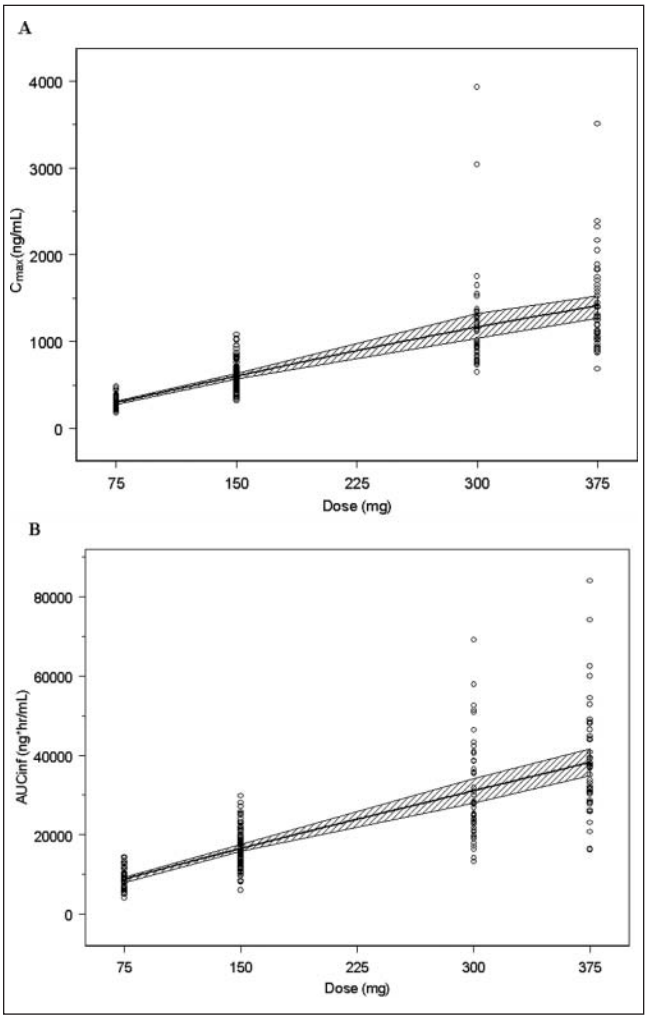

Figure 4. Relationship between the extent of trazodone systemic exposure and dose after oral administration of single doses of TzCOAD ranging from 75 to 375 mg to healthy subjects under fasting conditions. The circles are the individual observed values, the solid line is the fitted value based on the power model, and the shaded area is the 90% confidence interval. (A) Trazodone maximum plasma concentration (C_{max}). 234 × 196 mm (96 × 96 DPI). (B) Trazodone area under the plasma concentration-time curve from time 0 to infinity (AUCinf). 235 × 188 mm (96 × 96 DPI).

about the relationship between the pharmacokinetic parameters and the dose. The disadvantages of this method are that each dose is considered a separate treatment, the ordering of doses is not taken into account, and potential problems are presented with multiple comparisons.[33] By contrast, the power model takes into account the order of doses and, unlike the former approach, evaluates data from all the doses simultaneously, thereby increasing the statistical power of the analysis.

These 2 methods were used to assess the dose proportionality of TzCOAD 150-mg and 300-mg scored extended-release caplets following administration of bisected and intact caplets at doses ranging from 75 to 375 mg. Using the bioequivalence approach, dose proportionality was declared if the (1-α)% confidence intervals for the ratio of geometric mean values for dose-normalized C_{max} and AUC were contained completely within the acceptance range (θ_L-θ_H),[34] and $\alpha = 0.1$, $\theta_L = 0.80$, and $\theta_H = 1.25$ in the current FDA guidance.[29] Thus, the bioequivalence approach leads to a dichotomous outcome for each pairwise comparison—the drug product strengths are dose proportional or they are not. It has been suggested that the assessment of dose proportionality is a problem of estimation rather than of hypothesis testing.[33] Estimation of the magnitude of deviation from dose proportionality provides the necessary information. However, treating dose as a continuous variable requires a mathematical model. The power model is able to detect nonlinearity and to estimate its magnitude and is generally recommended as the best approach, providing there is no evidence of lack of fit.[36]

In the current study, dose proportionality was generally concluded because all but 2 of the treatment comparisons (1 for trazodone, 1 for mCPP) met the acceptance criteria. When the bioequivalence approach was used, the mean dose-normalized C_{max} for trazodone was 19.7% higher for the half 300-mg caplet compared with the intact 300-mg caplet. The resulting upper limit of the 90% confidence interval for dose-normalized C_{max} (110.5%-129.8%) was higher than the acceptance limit of 125%. However, the bioequivalence assessment for C_{max} for the 375-mg dose (which also used a scored caplet) did establish proportionality. Furthermore, the bioequivalence assessments of mCPP for the bisected caplets showed proportionality. For mCPP, the treatments were proportional with respect to peak and total systemic exposure, with 1 exception. The dose-normalized C_{max} for mCPP was 14.3% lower for the 150-mg intact caplet compared with the 300-mg intact caplet. Thus, dose proportionality could not be concluded for peak mCPP exposure because the lower limit of the 90% confidence interval for dose-normalized C_{max} (77.8%-94.3%) fell below the lower acceptance limit. That said, the study was powered based on the variability of AUC and C_{max} of the parent drug, not the metabolite. As recommended by FDA, metabolite data were provided for information only.

Results of the assessment based on the power model confirmed that dose proportionality can be claimed for C_{max}, $AUC_{0\text{-}t}$, and $AUC_{0\text{-}\infty}$ for both trazodone and mCPP across the entire range of doses evaluated in this study (ie, 75-375 mg).

The loss of the controlled-release properties following caplet splitting may pose serious risks for patients. Results obtained with complete tablets and half tablets of SR theophylline, acetylsalicylic acid, and diltiazem formulations showed that the division affected the dissolution characteristics.[37] In general, splitting of the tablets resulted in faster drug release, perhaps due to increased surface area exposed by breaking the tablet.[37] Therefore, in this study, the proportionality of bisected and intact caplets was assessed. Examination of the mean trazodone concentration-time profiles following dosing with half 300 mg and intact 150 mg shows that the peak concentration for the half 300-mg dose group is later than for the intact 150-mg caplet. This delay to peak concentrations would not be expected to have occurred if bisecting the caplet had resulted in a loss of the controlled-release properties of the caplet. Although dose proportionality could not be claimed for C_{max} for the half 300-mg caplet compared with the intact 300-mg caplet, all other related assessments indicated that dose proportionality could be claimed for the bisected caplet. It was concluded that splitting TzCOAD caplets does not significantly affect the controlled-release properties of the formulation.

Dose proportionality was concluded over the dose range evaluated in this study. These results contradict previous findings suggesting that trazodone may have nonlinear pharmacokinetics due to saturation of its first-pass metabolism with increasing doses over the clinically relevant dosing range.[16] Because trazodone is a substrate of CYP3A4, its metabolism can be inhibited by CYP3A4 inhibitors such as ketoconazole, ritonavir, and indinavir, resulting in increased trazodone plasma concentrations.[35] Coadministration with inducers of CYP3A4 (eg, carbamazepine) may result in decreased concentrations of the parent drug and metabolite. Furthermore, because CYP2D6 is responsible for the metabolism of mCPP, caution should be exercised in co-prescribing inhibitors or substrates of CYP2D6 with trazodone.[12] Because the pharmacokinetics of intact and bisected TzCOAD caplets are dose proportional across the clinically relevant range of doses, potential drug–drug interactions should be predictable across that range.

Adverse events related to trazodone occur mainly when high doses are initially used or when the dosage is increased too rapidly.[38] Reformulating the

drug to control the rate of release of trazodone may improve tolerability by avoiding the early and relatively high peak plasma concentrations following administration of immediate-release formulations. No once-daily trazodone formulations are currently marketed. However, a prolonged-release formulation of trazodone HCl (Trittico AC, Angelini, Rome, Italy) is marketed in Europe as a twice-daily product.[38] The pharmacodynamic effects and pharmacokinetic characteristics of the 150-mg prolonged-release formulation were compared with those of a 150-mg dose of the immediate-release comparator. The AUC was not statistically different from that of the conventional formulation. However, C_{max} was 20% lower with the prolonged-release product (1200 ± 389 ng/mL compared with 1710 ± 179 ng/mL) and T_{max} was delayed (4 hours compared with 2 hours). The half-life was 12 hours for the prolonged-release tablet, compared with 7 hours for the immediate-release formulation. Adverse events after 150-mg immediate-release trazodone were more frequent and more severe than after the same dose of prolonged-release trazodone, and their occurrence was related to plasma trazodone concentrations. Monteleone and colleagues[38] demonstrated that lowering peak plasma trazodone concentrations with a controlled-release formulation resulted in a significant reduction in both frequency and severity of adverse events in healthy subjects.

In the current study, single doses of TzCOAD up to 375 mg were well tolerated in 45 healthy subjects. Overall, the increasing incidence of the most commonly reported adverse events with dose (Table III) was statistically significant ($\chi^2_4 = 15.4$, $P = .004$). However, for each adverse event, the incidence across doses was too low to yield valid statistical results, with the exception of headache, which did not show a significant dose effect ($\chi^2_4 = 4.8$, $P = .30$). The safety and tolerability of TzCOAD were confirmed in a randomized, placebo-controlled study in which 202 patients with major depressive disorder received daily doses of TzCOAD ranging from 150 to 375 mg over a 6-week treatment period.[19]

TzCOAD caplets may potentially improve tolerability further because a lower mean C_{max} (531 ± 143 ng/mL) was obtained at a median of 6 hours following single-dose administration of an intact 150-mg caplet. It is a reasonable hypothesis that a lower frequency of adverse events attained by a controlled-release formulation of trazodone may improve the compliance of depressed subjects and result in more favorable outcomes.

CONCLUSIONS

TzCOAD extended-release caplets exhibit linear pharmacokinetics over doses ranging from 75 mg to 375 mg and maintain their controlled release properties when the caplets are bisected along the score line.

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